Diversity, Stability, Recursivity, and Rule Generation in Biological System: Intra-inter Dynamics Approach

Kunihiko Kaneko

Department of Pure and Applied Sciences, College of Arts and Sciences,

University of Tokyo,

Komaba, Meguro-ku, Tokyo 153, Japan

Abstract

Basic problems for the construction of a scenario for the Life are discussed. To study the problems in terms of dynamical systems theory, a scheme of intra-inter dynamics is presented. It consists of internal dynamics of a unit, interaction among the units, and the dynamics to change the dynamics itself, for example by replication (and death) of units according to their internal states. Applying the dynamics to cell differentiation, isologous diversification theory is proposed. According to it, orbital instability leads to diversified cell behaviors first. At the next stage, several cell types are formed, first triggered by clustering of oscillations, and then as attracting states of internal dynamics stabilized by the cell-to-cell interaction. At the third stage, the differentiation is determined as a recursive state by cell division. At the last stage, hierarchical differentiation proceeds, with the emergence of stochastic rule for the differentiation to sub-groups, where regulation of the probability for the differentiation provides the diversity and stability of cell society. Relevance of the theory to cell biology is discussed.

1 Introduction: Life as Complex Systems

A biological system generally consists of diverse elements, which, as a total, has ability of reproduction. In other words, a set of elements should reproduce itself, although the reproduction must be rather loose and inaccurate, when one imagines a prototype of Life. To have such reproduction process efficiently, it is expected that there are strong interactions among elements, since the reproduction should involve positive feedback process, which leads to nonlinear dynamics with instability in orbits. As has been studied in nonlinear dynamics with many degrees of freedom, the diversity of element states is then expected. In this sense one can expect that the diversity exists at the first stage of Life. In general, (i) *mechanism to create the diversity* is the first important question to be answered in the study of theoretical biology. These diversified elements form an ensemble, which often keeps some sort of stability, as an ensemble. Organization of such higher-level is seen in a multi-cellular organism and ecosystem. (ii)*Mechanism of the formation of a higher (ensemble) level keeping stability* is the second question to be answered.

However, diversity and complexity are not same. As for complexity, some semantic structure is necessary. In other words, the emergence of rules leading to a structure is required, and furthermore, subjective individual to distinguish the world as complex rather than random is postulated [1]. Then the following two questions are raised; (iii) *how a rule is formed from the mess of mutual relationships*, and (iv) *how an individual unit is formed to separate it out from the remaining world*. (Possibly these two are related).

These four basic questions lead to more specific ones. In spite of the tendency forming diversity, (v)*how is a set of discrete types formed*? Cells in a multi-cellular organism are grouped into distinct types, although any cell in the same type is slightly different. Several distinct types of organisms seem to be formed (even in a uni-cellular organism), as may be called 'species', although the present definition of species by sexual separation may not be applied. Some of these types of states are stable against reproduction, that is, a same type of unit is formed by the reproduction. For example, in the cell differentiation process, cells are diversified at the initial stage to several types, and later are determined to keep the distinct cell types (i.e., to have recursiveness). Thus (vi)*the origin of recursive states* is the next question to be answered. Note that these types are not predetermined, and the varia-

tion within the type can lead to further differentiation. This differentiation process is temporally organized in a tree-like structure, and sub-types with smaller difference is also formed. Now (vii) *the question of hierarchical differentiation* is raised, as is seen in cell differentiation process, and possibly in the evolution.

Now let us come back to the question (iv), where we note that the separation cannot be complete, since we live in interacting world. Forming a good interface to cut the individual from the outer world is the only possibility. How is this possible? Each individual unit must have information of the outer world embedded within it. The interface forms a mutual relation between the whole and individual; the whole consists of individuals, but the property of an individual is also governed from the higher (ensemble) level of elements (whole). This mutual feedback process, which is a key issue in complex system studies, may be termed as a kind of complementarity between the whole and part (individual). In the study of complex systems, we search for a mechanism (iix)*how a global information on the ensemble of elements is embedded into each individual one*.

When one considers a problem of biology, we have often seen complementarity between two groups: Roughly speaking, one group is characterized by symbol, rule, syntax, discreteness, and part, while the other by pattern, behavior, semantics, continuity, and the whole.

The current trends in molecular biology aim to explain the latter from the former. In the study of development, one is interested in how a set of instructions given by digital information on DNA leads to the body of complex organisms. On the other hand, such instruction itself should have been evolved through the history of life, as long as one does not assume the "designer" of Life. In this context it is meaningful to ask the reverse question mentioned at (iii), rephrased as; *How is a set of syntactic rules formed from complex developmental process*?

The complementarity between the above two groups is often discussed in quantum-mechanical context. Indeed some believe that quantum mechanics is essential to biology. However the concept of complementarity itself is not necessarily associated with quantum mechanics, but is more general[2]. In the study to be pursued here, we try to demonstrate that interacting dynamics of internal states leads to such complementarity by allowing for autonomous change of the rule of the dynamics itself.

Now let us come back to the problem (iv) on the formation of unit:

Units do not exist a priori. These are formed through interactions. Since the behavior is diverse enough and the separation of units from the outside is not complete, the units cannot be completely identical. For example, all cells are not identical in contrast with an elementary particle in physics. A biological system is essentially heterogeneous. The importance of heterogeneity lies in the ability to map the outer world into a unit, which again comes to the problem (iix) (*embedding global information into each individual unit*). In the development, cells, besides their distinct types, have global information on their position, possibly represented in their modulation. This is why we adopt dynamics with a continuous state later, instead of discrete-state dynamics like cellular automata.

The hierarchy in a heterogeneous system is different from that in a homogeneous system. According to (iix), the information on an ensemble can be embedded into the variation of units of the same type, and the relation between the ensemble and unit is bidirectional. This hierarchy continues further. A tissue consisting of cells, for example, is differentiated. Now we have to answer (ix)*how the formed, higher-level ensemble again acts as a unit for diversification and differentiation*. This higher-level unit works as a unit for reproduction. Thus the last question to be addressed is (x) *the origin of individuality, which reproduces itself at an ensemble level*.

Let us sum up the postulates that should be answered as complex systems studies for biology.

- (i) mechanism to create diversity
- (ii) the ability to form a higher level unit consisting of an ensemble of the original units, stable as a state at each instant and also through developmental process
- (iii) formation of a syntactic rule from complex mutual relationship
- (iv) formation of a unit to separate it from outside
- (v) formation of discrete states leading to (cell) types, and also analogue modulation of the state
- (vi) recursivity of a state, preserved by the reproduction

- (vii) hierarchy of differential process, characterized in the time course and also in the phenotype space
- (iix) mechanism to map the global information (on ensemble) to each individual unit
- (ix) higher level of differentiation
- (x) formation of a higher-level reproduction unit

In the cell biology [18], the above list corresponds to (i) diversity of cells (ii) formation of cell society, leading to multi-cellular organisms or tissues where developmental and ongoing stability of the cell society is sustained (iii) formation of a correspondence between genetic information and phenotype, and later the emergence of cell differentiation rule (iv) origin of a cell with a membrane that suitably separates it from the outside (v) formation of discrete cell types with modulation within each type of cell (vi) determined cell differentiation (i.e., formation of cell type keeping its type) (vii) hierarchy of differentiated cell types, both in the developmental course and in the difference of cell characters (iix) modulation of cell character in each type of cell, reflecting on the surrounding cells (or number distribution of cells of each type in the ensemble) (ix) differentiation of an ensemble of cells (tissue), and (x) ensemble of cells acting as the reproduction unit, in other words, the reproduction of multi-cellular organism, and the formation of individuality.

It should be noted that (most of) the above problems are essential to a biological system in general, not only to a cell society but also to neural and immune networks, society of organisms, dynamical stability of ecosystem, evolution of language, and so forth.

2 Intra-inter dynamics

What type of model should one adopt to capture the above constraints? In a biological system it is important to capture the interplay between inter-unit and intra-unit dynamics [3]. Such "intra-inter dynamics" is essential to cell biology, where complex metabolic reaction dynamics in each unit (cell) is affected by the interaction among cells. An ecological system also consists of interacting units with internal dynamics. In neural systems also, the intra-inter dynamics is relevant to the formation of internal images.

Another missing factor in conventional dynamical systems studies for modeling biology is the "fluidity" of dynamical systems itself. In a dynamical system approach, we have a set of variables to represent states, the rules of their temporal evolution and, initial and boundary conditions of them. The rules and initial and boundary conditions are given in advance and fixed independently of the change of state variables. In biological problems, such independence may not be valid. For example, the number of variables itself changes with time, through, for example, by cell divisions and cell deaths. In developmental process, initial and boundary conditions of states are chosen so that the reproduction continues, from their mother's states.

In our approach we allow for "dynamics of dynamics". For example, the change in the degrees of freedom is allowed, where formation of a unit acting as a "partial system" is possible, which selects its initial and boundary conditions.

As a specific example of the scheme of intra-inter dynamics, let us consider cell differentiation. Here a set of chemical concentrations in a cell is chosen as the state variables. Internal dynamics consists of several biochemical reaction processes, while there exists cell-to-cell interaction through diffusion of chemicals and other signal transmission. The change of dynamics itself is due to the cell division and death depending on the cellular state, by which the number of degrees of freedom varies. We will see that a rule at a higher level for cell society is formed from complex dynamical behavior arising from the lower level (biochemical) dynamics.

Now the remaining questions are the choice of internal dynamics, interaction, and division process. We have several possibilities in the choice, and the model can be classified according to the complexity of the three processes; (a) the degrees of freedom in each cell and the form of the internal dynamics, (b) form of cell-to-cell interaction, and (c) meta-dynamical structure to change the cell numbers.

First, it may be interesting to reconsider previous models on cell biology from the present viewpoint. In the pattern-formation mechanism of the Turing instability mechanism [4], the internal dynamics is not so well defined, although it provides the most important step for the interaction-based approach in cell differentiation. As for the level of internal dynamics there are two pioneering studies. The importance of temporal oscillations in cellular dynamics was stressed by Goodwin[5] (see also [6]). Diverse cell types were attributed to coexistence of many attractors by Kauffman [7], by adopt-

ing Boolean network dynamics (cellular-automaton type dynamics). Here cell-to-cell interaction is neglected, while some efforts to include them are discussed following the Turing instability mechanism. In these models, no meta-dynamical structure is included.

In these few years, we have studied several models of the above intra-inter dynamics[8-13]. We choose a set of chemical variables to assign each cellular state. As for the internal dynamics we assume some oscillatory dynamics. So far we have studied ;(see also Table I)

- (A) phase dynamics with instability (for example by the circle map of the phase $\theta_{n+1} = \theta_n + (K/2\pi)sin(2\pi\theta_n)$ [8, 9]
- (B) multi-phase dynamics given by a coupled circle map [9]
- (C) simple oscillatory dynamics with three chemicals[10]
- (D) oscillatory dynamics with several chemicals adopting auto-catalytic reactions [11, 12]
- (E) chaotic dynamics with several chemicals adopting auto-catalytic reactions [13].

Table I

Model	Degrees of freedom	Internal	Differentiation
(A)	phase	circle map	growth speed
(B)	multiple phases	coupled circle map	chemical role
(C)	phases and amplitudes	simple oscillation	amplitude
(D)	phases and amplitudes	oscillation	determined
(E)	phases and amplitudes	chaos	hierarchy, higher-level

In the models (C)-(E), there is a set of chemical variables, and bio-chemical network within each cell, whose concentration changes according to Michaelis-Mentens type catalytic reaction, where chemicals catalyze each other, or themselves.

As for the interaction range, we have studied global interaction with a homogeneous all-to-all coupling mostly, but have also studied local coupling among cells within a given range. In the former case, cells are assumed to

interact with each other through the media. For the interaction form, we have adopted active transport process to get resources, for (A)-(C), the diffusion process for (E), and both for (D). The active transport here means that the ability to get chemicals from the media depend on the chemicals in a cell. Nutrition chemicals are slowly poured into the media, and the interaction between cells leads to competition for nutrition chemical.

The cell division is assumed to occur when some chemical products (e.g., membrane or DNA) are accumulated beyond some threshold, or a cell volume calculated from the chemicals within becomes twice. For both cases, the condition is of an integral-type. In the former case, the threshold condition is given as an intergal of some chemicals concentration, while for the latter case, the cell volume is expanded through the transport of chemicals into it, until the cell divides into two. For the 'abstract' phase models of (A) and (B), the condition is not such straightforward. Here it is given by the threshold for the accumulated number of rotation of phases, since the rotation of phase in the model is brought about by the flow of nutrition term in each cell. For all models, the concentrations of chemicals of two divided cells are chosen to be almost identical upon the division.

The death condition is also determined by a cellular state (e.g., if the total amount of chemicals is less than some threshold, the cell dies). The cell death process usually sets in at a later stage of developmental process, where the competition for resources is higher.

For all the models, diversification of cells and grouping of cells by the clustering of phases of oscillators are observed. In the model (A), inactive cells without division and rapidly replicating cells are separated at some temporal regime. In (B), roles of chemicals also differentiate, while the two temporal regimes alternate, one with a society with diverse cells, and the other consisting of a homogeneous cells. In (C), the amplitudes of cellular oscillations differentiate to large and small ones, and the stability of an ensemble of cells is found. In the present paper we generalize the results obtained in the model (D) and (E).

Before describing the scenario of the differentiation extracted from the simulations, we note two backgrounds of the theory, one from dynamical systems and the other from experiments.

The scenario is based on the study of globally coupled chaotic systems [14]. In the study, tiny differences among the elements are amplified through chaotic instability, which then leads to dynamical clustering of the elements.

The temporal pattern of the clustering is robust against external noise or is deterministic even if differences in the initial state are given stochastically. Our model takes into account of the feature of the globally coupled chaotic system, although the internal dynamics in the model (D) is not necessarily chaotic. On the other hand, the change in the degree of freedom is brought about by the cell division in the course of cell differentiation. Hence the dimension of the phase space is no longer fixed, and the orbital instability there cannot be characterized by ordinary dynamical systems, and we may encounter the situation what we call open chaos [8, 15].

On the other hand, stability at an ensemble level is studied as collective dynamics in globally coupled maps [16]. By including meta-dynamics (dynamics to change the parameter), dynamic stability to keep the diversity is found, and the concept of 'homeochaos' is proposed [17].

Although our goal is the reinterpretation of the cell biology [18] from our intra-inter dynamics viewpoint, it may be interesting to point out two specific experimental results here. Yomo and his colleagues reported that even under single external condition, the cells differentiate to some distinct physiological states [19]. In their experiment, it was shown that one cell type of E. coli resulted in a population with several distinct cell types after successive cultivation in a well-stirred liquid culture. Even under the same initial and external conditions, the cells autonomously differentiated.

Rubin [20] and his collaborators have shown that a cell line from mouse epigenetically transforms to different types of foci in size under the same condition. In addition, the frequency of transformation and types of the transformed cells were shown to depend on the cell density and the history of the cell culture. This suggests that transformation or differentiation of cells is dynamically generated by inter-cellular interaction.

3 Isologous Diversification

From several simulations of the model starting from a single cell initial condition, Yomo and the author proposed the following "isologous diversification theory", as a general mechanism of spontaneous differentiation of replicating biological units [10, 11, 12], which is extended in [13] by adopting a model class (E). Starting from a single unit, the following process of differentiation occurs.

(1) Synchronous oscillations of identical units

Up to some number of cells, all cells are identical as to the chemical concentration, which oscillate coherently. Accordingly, the cells divide almost simultaneously, and the number of cells is the power of two.

(2) Differentiation of the phases of oscillations of internal states.

When the number of units exceeds some number, they lose identical and coherent dynamics. Although the number depends on the choice of network and the parameters, the loss of synchrony generally appears in order to see continuous growth in cell numbers. Then cells separate into several groups whose phases of oscillations are close. At this stage, only the phases of oscillations are different by cells, but the temporal averages of chemicals, measured over periods of oscillations, are almost identical. The behavior here is due to the clustering of phases studied in coupled nonlinear oscillators. As has been discussed [8, 10], this temporal clustering provides time sharing for resources: Cells can get chemical resource successively in order by the difference of phase of oscillations, because the rate of the transport of resources into a cell depends on the chemicals within.

(3) Differentiation of the amplitudes of internal states.

After some divisions of cells, differences in chemicals start to be fixed by cells. The average chemical concentrations and their ratios differ by cells, even after taking the temporal average over periods. Thus the behavior of states is differentiated to some types. The orbits of chemical dynamics lie in a different phase space region by types of cells.

It is also interesting to note that the frequency of oscillations is also differentiated. One group of cells oscillates and divides faster than the other group. Hence the differentiation of inherent time scales of cells emerges spontaneously through cell divisions.

(4) Transfer of the differentiated state to the offsprings by reproduction.

After fixed differentiation, chemical compositions of each group are inherited by their daughter cells. Cell state represented by average chemical composition remains to be identical by division, and thus the cells keep the "recursivity" by divisions. It is important to note that the chemical characters are "inherited" just through the initial conditions of chemical concentrations after the division, although we have not explicitly imposed any specific mechanisms to keep the type.

The determination of a cell has occurred at this stage, since daughters

of one type of cells preserve the type. By reproduction, the initial condition of units is determined to give the next generation of units of the same type. Thus a kind of memory is formed, attained through the transfer of initial conditions on chemical concentrations by the cell division.

The cellular memory at this fourth stage is formed as a result of the selection of initial conditions for a cellular state (i.e., a partial system of the total dynamical system). One might think that this selection is nothing but a choice of basin of attractions for a multiple attractor system. If the interaction were neglected, this would be basically correct. In our case, this is not true. Indeed most of the dynamical states of cell types do not exist as an attractor but are stabilized through interaction. The observed memory lies not solely in the internal states but also in the interactions among the units.

To see this intra-inter nature of the memory explicitly, one effective method is the transplantation experiment. Numerically, transplantation experiments are carried out by choosing determined cells (obtained at the normal diffusion process) and putting them into a different set of surrounding cells, and making a cell society that could not appear through the normal course of development.

When a determined cell is transplanted to another cell society with different cell type distribution, the offspring of the cell remain to be of the same type, unless the cell-type distribution of the society is strongly biased (i.e., the ensemble consisting of the same type of the cell as transplanted). The cell memory is preserved mainly in each cell, but suitable cellular interactions are also necessary to keep the stability. Generally speaking, internal cellular memory is maintained as long as the diversity is sustained. The achieved recursivity is understood as the choice of internal dynamics through cellular interactions.

(5) Hierarchy of organized groups.

As the cell number increases, further differentiation proceeds. Each group of cells further differentiates into two or more subgroups. Some cells behave as a stem cell to support further differentiated cells.

For example, six types ("0","1","2","1a",1b"1c") of cells are found in [13]. The differentiation rule here is found to obey ($0 \rightarrow$ 0,1, or 2; $1 \rightarrow$ 1,1a,1b,or 1c; $2 \rightarrow 2$, $1a \rightarrow 1a$, $1b \rightarrow 1b$, and $1c \rightarrow 1c$, in the normal course of differentiation starting from a single cell). Hierarchical rule of differentiation is thus generated. Although the number of cell types and the

rule of differentiation depend on the choice of chemical networks, generation of a hierarchical rule (written by the tree-type diagram constructed from the above rule) is generally observed, in a class of models (E).

Thus differentiations obey a specific rule, which is given as a change of internal states but depends on the dynamical interaction among cells. The rules of differentiation and the higher level dynamics emerge as the interaction of cells with internal dynamics.

Often the switching of cell types to further subgroups are given by a stochastic automaton rule, where the stochasticity is supported by the chaotic intra-cellular dynamics[13]. The rate of the differentiation or the replication (e.g., the choice which arrow from $0 \to 0, 1, 2$ is selected) depends on the cell-type distribution. For example, when some of type-1 cells are removed, the differentiation rate $0 \to 1$ increases. With this regulation mechanism to recover the decreased cell type, the stability of the distribution of cell types is kept. The global stability of the whole system is thus obtained, by spontaneous regulation of the rates of the differentiations.

(6) Formation of higher level dynamics and diversity of cell groups

Since the rule of differentiation depends on the distribution of other cell types, one can get an approximate dynamics for the population of each cell type. This is a higher level than a cell type from chemicals, i.e., tissue from cell types. This population-level dynamics is stochastic, since the information on the number of cell types is not complete, where the lower-level information on the internal state (of chemical concentrations) is discarded. It is interesting to note that the macroscopic flow chart on the number of cell types is formed in spite of the stochasticity.

In some models [13], we have found that this higher level dynamics allows for several stable states, implying the coexistence of several stable cell distributions. Indeed, in the models, we have found different sets of cell distributions, starting from a single cell, depending on its initial condition. Thus we have found that the cell colony is also diversified and differentiated to few groups.

4 Discussion

Let us discuss how the initial ten problems are resolved (or remain unsolved) in our intra-inter dynamics approach.

- (i) Diversification due to orbital instability in each internal dynamics (open chaos)

  In our study, the diversity is created through the orbital instability in dynamical systems. Chaotic *attractor* is not necessarily required, since the transient dynamics with instability, in conjunction with the change of degrees of freedom, is often sufficient to provide the diversity.

  As a corollary of this mechanism, relevance of chemicals with low concentration is expected, since tiny difference of "rare" chemicals between two cells is amplified to lead to a macroscopic difference between them. In our simulation, chemicals with tiny amounts in cells are relevant to the trigger to differentiations. It should be noted that this relevance of chemicals with low concentrations is also supported in physiological facts. Even at differentiated cells, difference is most remarkable for chemicals with low concentrations.

- (ii) Stability of an ensemble level, partly provided by collective dynamics of coupled nonlinear elements

  Stability at a macroscopic level has been discussed in dynamical systems theory, where dynamics of an ensemble of chaotic elements keeps some stability through the interaction [16, 17]. In our simulation, removal of several cells of a given type enhances the differentiation to the removed type, which restores the original ratio of types of cells. This macroscopic stability assures the robustness of developmental process against perturbations including somatic mutations.

- (iii) Formation of a syntactic rule, partly by the rule for chaotic itinerancy; (which, however, waits for other mechanisms to be clarified)

  The deepest question in this topic is the formation of semantic-syntactic correspondence such as the phenotype-genotype one. So far we have not succeeded in constructing a coherent scenario for it within our intra-inter dynamics, although in a model of a class (E), differentiation of chemicals between slow, inactive, and controlling variables and

fast, and controlled variables with chaotic dynamics are found, which may support the postulate by corresponding the former to the role of genotype and the latter to the phenotype[21].

The problem we have addressed in the present paper is much simpler; the formation of differentiation rule. As is discussed later at (v), each cell type is represented as a state in the phase space of the internal dynamics. The transition rule is given by the switching among these states, through interactions. A related mechanism for the formation of the switching rule has been discussed in chaotic itinerancy [14, 22, 23]. It is long-term dynamics with itinerancy over several states through chaotic dynamics, often found in high-dimensional dynamical systems. For our switching rule, we do not have clear dynamical systems representation, since it is also interaction dependent, although the understanding of chaotic itinerancy[24] may give a step towards the rule formation.

- (iv) Formation of a unit to separate it from outside: (not yet discussed)

  Since we have assumed the existence of a cell, separated out by a membrane, this question cannot be discussed as yet, although it is essential when one considers the origin of life [25].

- (v) Formation of discrete (cell) types, first provided by clusterings, and then by attracting states stabilized by the interaction

  After the diversification of cell states, they are grouped into several types. Such grouping of oscillators by their phases is first studied as clustering in coupled map system at the stage (2). Then the cells split into several groups whose orbits lie in different parts in the phase space. Here these states are represented as attracting states stabilized by the interaction. Only a discrete set of states exists, stable against perturbations, cell divisions, and the variation of interaction in the natural course of differentiation.

  Difference of the phases of oscillations by the clustering is given by "analogue" means, and cellular states at any phase of oscillations can exist in principle. On the other hand, the differentiation based on the phase space position is digital, in the sense that only discrete levels are allowed. Hence there are two levels of differences by cells, one

for the change of phases of oscillations, and the other for the fixed differentiation.

Note that the differences by phases of oscillations are not rigid, since the phase is easily diffused by external disturbances: Perturbations brought about by division are enough to shift the phase and destroy the memory of the previous clustering. On the other hand, the "digital" difference by the amplitude of oscillations is more rigid, since it is not shifted continuously as in the case of phase. This emergence of digital information is the basis of the cellular memory at (vi).

- (vi) Recursivity of a state, preserved by the reproduction, as a choice of initial conditions with digitalization of differentiated states

  The recursive character of states is attained as the transfer of initial conditions by cell divisions, so that the dynamics later remains to be attracted to the same type. Such attraction is supported by the interaction. When the cellular state is disturbed, the intra-inter dynamics works to restore the orbit to have the recursivity. The "digital" distinction of chemical characters, that has emerged at (v), is relevant to preservation of the characters to daughter cells, since analogue differences of phases may easily be disturbed by the division process, and cannot be transmitted to daughter cells robustly.

  In biological terms, the recursivity corresponds to determination of differentiation. Our picture implies that there are levels of robustness of this determination. Since the stability of states is given as a balance between internal dynamics and the interaction, the robustness against the external change is larger as the internal dynamics plays more role for the determination of the state.

- (vii) Hierarchy of differential process, supported possibly by hierarchical structure in a coupled chaotic system

  We have observed the hierarchical differentiation, as a successively smaller structure in the phase space[13]. We have not yet clarified the condition to have such hierarchical structure in the phase space, but it should be noted that (transient) chaotic dynamics often provides a hierarchical structure, as is studied in globally coupled maps[14].

- (iix) Mechanism to map the global information to each individual unit, provided by the interaction-induced modulation

  As mentioned, two types of memory coexist, analogue and digital ones. The former gives information on the cell society, i.e., the distribution of cell types, while the latter gives a distinct internal state on cell differentiation. Indeed the orbits of chemicals of each cell type are shifted slightly with the change of the distribution of cells surrounding it. Gobal information on the cell distribution is embedded into this 'analogue' change, which modifies the rate of differentiation. Now one can see how the complementarity in §1 between analogue/whole and digital/part is given by the intra-inter dynamics approach.

  We believe that such dual memory structure is a general feature in a biological system, that exists as an interface between external environment and the internal dynamics. In cell biology, the "analogue" difference reflecting on the interaction is known as modulation [18]. According to our theory, this modulation determines the rate of differentiation, and leads to the stability of cell society.

- (ix) Higher level of differentiation by the formation of higher-level dynamics supporting the instability and several stable states

  According to the mechanism (vii), there appears a higher level dynamics for the population of cell types. This higher-level dynamics can again have instability to provide the diversity and the stability to attract several states. Although a few examples in model class (E) support this differentiation of cell society, the condition to form this higher level is not clear yet.

- (x) Formation of a higher-level reproduction unit by forming an interface structure to separate an ensemble of units from other units

  The origin of a multicellular organism, for example, is directly related with our scenario. For its origin, some mechanism of differentiation of identical cells is necessary which leads to divisions of labor. In our theory, this mechanism is naturally explained. Such differentiation generally appears, for cells to increase their number within limited resources. Indeed, the number of cells stops at a small level in our

simulation, when the internal chemical reaction network does not allow for the clustering of oscillations and the state differentiation.

However, this mechanism is not sufficient for the origin of a multicellular organism. The ensemble of cells as a whole should reproduce as a recursive unit. To study this origin of a higher level unit, we have studied a spatial version of our models (A) and (D). Instead of global interaction, we have chosen local interaction only within a range, and also added the mobility of cells according to the inter-cellular force depending on cellular states. When the ranges for chemical interactions and for inter-cellular force are of comparable order, the cells continue dividing and spread over the space, by forming a spatially localized set of cells, acting as a unit for reproduction[26].

Summing up, we have proposed intra-inter dynamics to provide a new viewpoint to cell biology. We believe that the present theory can generally be applied to a variety of biological systems, because it is based on our study of coupled dynamical systems, which is expected to be universal in a class of interacting, reproducing, and oscillatory units. So far we believe that the proposed theory captures the essence of cell differentiation, such as the loss of totipotency, origin of stem cells, differences in growth rates, and developmental stability, and so forth. Apoptosis and tumor formation are also discussed in the present interaction-based picture [12]. Indeed, the "tumor"-like cell is found in the model (D)[12], as is characterized by extraordinary differentiation, loss of internal chemical diversity, faster growth, and destruction of the diversity of cells. Indeed formation of "selfish" cells destroying the diverse cell society is expected, when a suitable condition of the interaction is lost, since our differentiation process is not programmed explicitly as a rule but occurs through the interaction in our theory.

acknowledgments

The present paper is based on the studies in collaboration with T. Yomo and C. Furusawa. I am grateful to them for stimulating discussions. I would also like to thank S. Sasa and T. Ikegami, for discussions and Y. Oono for criticisms. The work is partially supported by Grant-in-Aids for Scientific Research from the Ministry of Education, Science, and Culture of Japan.

References

[1] K. Kaneko and T. Ikegami, *Life as Complex Systems* (tentative title), in preparation, (in Japanese, to be published from Asakura pub.)

[2] N. Bohr, *Atomic Physics and Human Knowledge*, John Wiley, 1958

[3] A prototype of the intra-inter dynamics is given by coupled map lattice: K. Kaneko, Prog. Theor. Phys. 72 (1984) 480; *Theory and Applications of Coupled Map Lattices* (Wiley), 1993 (ed. K. Kaneko), and references cited therein

[4] A.M. Turing, Phil. Trans. Roy. Soc. B, 237 (1952) 5

[5] B. Goodwin, "Temporal Organization in Cells", Academic Press, London (1963).

[6] B. Hess and A. Boiteux Ann. Rev. Biochem. 40 (1971) 237

[7] S.A. Kauffman, J. Theo. Biology. 22, (1969) 437

[8] K. Kaneko, Physica 75 D (1994) 55

[9] K. Kaneko, Physica 103 D (1997) 505; and unpublished

[10] K. Kaneko and T. Yomo, Physica 75 D (1994) 89

[11] K. Kaneko and T. Yomo, in *Advances in Artificial Life*", Springer (1995) 329 (eds. E. Moran et al.)

[12] K. Kaneko and T. Yomo, Bull. Math. Biol. 59 (1997) 139 and preprint

[13] C. Furusawa and K. Kaneko, submitted to Bull. Math. Biol.

[14] K. Kaneko, Phys. Rev. Lett. 63 (1989) 219; Physica 41 D (1990) 137; Physica 54 D (1991) 5; J. Phys. A 24 (1991) 2107

[15] K. Kaneko, Artificial Life 1, (1994) 163

[16] K. Kaneko Phys. Rev. Lett. 65 (1990) 1391; Physica 55D (1992) 368

[17] K. Kaneko and T. Ikegami,Physica 56 D (1992) 406

[18] e.g., B. Alberts, D.Bray, J. Lewis, M. Raff, K. Roberts, and J.D. Watson, *The Molecular Biology of the Cell*, 1983,1989,1993

[19] E. Ko, T.Yomo, I. Urabe, Physica 75D (1994) 84

[20] A. Yao and H. Rubin,, Proc. Nat. Acad. Sci. 91 (1994) 7712; M. Chow, A. Yao, and H. Rubin, ibid, 91(1994) 599; H. Rubin, ibid, 91(1994) 1039; 91(1994) 6619

[21] K. Kaneko and T. Yomo, to be published

[22] K. Ikeda et al., Prog. Theor. Phys. Suppl. 99 (1989) 295

[23] I. Tsuda, World Futures 32(1991)167; Neural Networks 5(1992)313

[24] K. Kaneko, Phys. Rev. Lett., 78 (1997) 2736

[25] Formation of an ensemble of molecules as a reproducing unit is studied, in an automaton model of moving tiles; T. Yamamoto and K. Kaneko, in *Advances in Artificial Life*, Springer (1995) 188-199 (eds. E. Moran et al.)

[26] K. Kaneko, in preparation